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On the graph and systems analysis of reversible chemical reaction networks with mass action kinetics

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Abstract— **Motivated by the recent progresses on the interplay between the graph theory and systems theory, we revisit the analysis of reversible chemical reaction networks described by mass action kinetics by reformulating it using the graph knowledge of the underlying networks. Based on this formulation, we can characterize the space of equilibrium points and provide simple dynamical analysis on the state space modulo the space of equilibrium points.**

I. Introduction

Recent progresses in the networked control systems and systems biology are a result of the interplay between the graph theory and systems theory. It results in the expanding literature on the analysis and control of multi-agent systems (we refer to [12] for a brief review) and on the analysis of biological systems, see, for instance, the reconstruction of gene regulation networks in [22], the synchronization problem in biological systems [17] and the new development in synthetic biology [13].

The analysis of chemical reaction networks using graph theory has previously been pursued by Othmer in [16], by Sontag in [18] and, recently, by Angeli *etal* in [1]. In these works, the chemical reaction networks are described by the mass-action kinetics and the stability analysis is done on the positive (or, forward) invariant subspace that is parametrized by the initial state. Feinberg in [7] gives perhaps the most comprehensive study on the dynamical properties of chemical reaction networks. Sontag in [18] explores an asymmetric weighted Laplacian matrix describing the network topologies for analyzing the dynamics of chemical reaction networks with the generalized mass-action kinetics (c.f., the formulation in [18, Section V]). Othmer in [16] presents equivalent representations of chemical reaction networks from various different perspectives, including, graph theoretical perspective and thermodynamical view.

In this paper, we revisit again the dynamics of reversible chemical reaction networks by reformulating it using the graph description of the underlying networks. Correspondingly, we can characterize the space of equilibrium points and provide simple dynamical analysis on the state space modulo the space of equilibrium points. In the literature of consensus or multi-agent systems, the state space modulo the space of equilibrium points is commonly referred to the disagreement vector. It is in contrast to the common approaches in the existing literature on chemical reaction networks that analyze the dynamics on a forward invariant subspace, the so-called *positive stoichiometric class*, which is parametrized by the initial state. Our result on the relation between the initial concentration to the unique final concentration is related to the recent concept of χ-consensus in [3].

In biochemistry, one often comes across a network of reversible chemical reactions consisting of several reversible reactions with common species and possibly common complexes. An example of a simple network of chemical reactions in the pyruvatic pathways is given below

$$\left.\begin{array}{l} \mathrm{Glu} + 2\mathrm{NAD} + 2\mathrm{ADP} \rightleftharpoons 2\mathrm{Pyr} + 2\mathrm{NADH} + 2\mathrm{ATP} \\ \mathrm{Pyr} + \mathrm{NADH} \rightleftharpoons \mathrm{Lactate} + \mathrm{NAD}. \end{array}\right\} \quad (1)$$

The compounds Glu, NAD, ADP, Pyr, NADH, ATP and Lactate involved in the reaction are called the species of the network. The combination of species $\big(\mathrm{Glu}+2\mathrm{NAD}+2\mathrm{ADP}\big)$ and $\big(2\mathrm{Pyr}+2\mathrm{NADH}+2\mathrm{ATP}\big)$ occuring on the left and right hand side of the first reaction are called the complexes of the first reaction. The reaction (1) proceeds changing the concentrations of the various species involved until a state of equilibrium is reached after which point the concentrations of the various species remain constant as long as there is no external flux of species affecting the reaction. In the example above, the dynamics of concentrations of the each of species involved in the network depend on both reactions. The most popular law governing the dynamics of the concentrations of the various species involved in a chemical reaction network is the *law of mass action kinetics*.

In order to derive a specific form of differential equations we will start with the basic assumption that the chemical reaction rates are governed by *mass action kinetics*. As an initial step we then derive a compact form of the dynamics involving a non-symmetric weighted Laplacian matrix of the complex graph. The basic form of these equations can be already found in the innovative paper by Sontag [18]. The main part of the paper is however devoted to a subclass of mass action kinetics chemical reaction networks, where we assume the existence of a thermodynamical equilibrium, or equivalently, where the *detailed balance equations* are assumed to admit a solution. We will call such chemical reaction networks *balanced chemical reaction networks*. Balanced chemical reaction networks are necessarily reversible but involve additional conditions on the forward and reverse reaction rate constants (usually referred to as the Wegschei-

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der conditions; see [9]). For such balanced chemical reaction networks we will be able to derive a particularly elegant form of the dynamics, involving a *symmetric weighted Laplacian matrix* of the complex graph.

The obtained form of the equations of balanced chemical reaction networks will be used to give, in a very simple and insightful way, a characterization of the set of equilibria, and a proof of the asymptotic convergence to a unique thermodynamic equilibrium corresponding to the initial condition of the system. Similar results for a different class of mass action kinetics reaction networks, in particular *weakly reversible* networks with zero-deficiency, have been derived in the fundamental work of Horn [10] and Feinberg [7], [8], which was an indispensable source of concepts and tools for the work reported in this paper.

The paper is organized as follows. In Section II, we summarize the mathematical structure of a network of chemical reactions described in [11], [7], [8], [16]. In Section III, we recall the law of mass action kinetics, and develop a mathematical framework that describes the dynamics of the species concentrations involved in a class of reversible chemical reaction network using the law of mass action kinetics, which we refer to as balanced mass action chemical reaction networks. It is shown in this section that our framework provides a number of tools for the analysis of balanced chemical reaction networks.

Notation: The space of $\mathtt{n}$ dimensional real vectors is denoted by $\mathbb{R}^{\mathtt{n}}$, and the space of $\mathtt{m}\times\mathtt{n}$ real matrices by $\mathbb{R}^{\mathtt{m}\times\mathtt{n}}$. The space of $\mathtt{n}$ dimensional real vectors consisting of all strictly positive entries is denoted by $\mathbb{R}^{\mathtt{n}}_+$ and the space of $\mathtt{n}$ dimensional real vectors consisting of all nonnegative entries is denoted by $\bar{\mathbb{R}}^{\mathtt{n}}_+$. $\mathrm{Rank}(A)$ denotes the rank of a real matrix A. Given $a_1,\ldots,a_n\in\mathbb{R}$, $\mathrm{diag}(a_1,\ldots,a_n)$ denotes the diagonal matrix with diagonal entries $a_1,\ldots,a_n$; this notation is extended to the block-diagonal case when $a_1,\ldots,a_n$ are real square matrices. $\ker(A)$ and $\mathrm{span}(A)$ denote the kernel and span respectively of a real matrix A. If U denotes a linear space, then $U^\perp$ denotes the complementary subspace of U (with respect to the standard Euclidian inner product). $\mathbb{1}_m$ denotes a vector of dimension m with all entries equal to 1. $\dot{x}$ for a vector x depending on time t will denote the time-derivative $\frac{dx}{dt}(t)$. Define the mapping $\mathrm{Ln}:\mathbb{R}^m_+\to\mathbb{R}^m,\quad x\mapsto\mathrm{Ln}(x)$, as the mapping whose i-th component is given as $(\mathrm{Ln}(x))_i:=\ln(x_i)$. Similarly, define the mapping $\mathrm{Exp}:\mathbb{R}^m\to\mathbb{R}^m_+,\quad x\mapsto\mathrm{Exp}(x)$, as the mapping whose i-th component is given as $(\mathrm{Exp}(x))_i:=\exp(x_i)$. Also, define for any vectors $x,z\in\mathbb{R}^m$ the vector $\frac{x}{z}\in\mathbb{R}^m$ as the element-wise quotient $\left(\frac{x}{z}\right)_i=\frac{x_i}{z_i},\quad i=1,\cdots,m$.

II. Chemical reaction network structure

In this section we will survey the basic topological structure of chemical reaction networks. First step is the stoichiometry expressing the conservation laws of chemical reactions. A next innovative step was taken in the work of Horn & Jackson and Feinberg [11], [7], [8] by defining the complexes of a reaction to be the vertices of a graph. We will summarize these achievements in a slightly more abstract manner, also making use of the exposition given in [16].

A. Stoichiometry

Consider a reversible chemical reaction network involving m chemical species (metabolites), among which r reversible chemical reactions take place. The basic structure underlying the dynamics of the vector $x\in\bar{\mathbb{R}}^m_+$ of concentrations $x_i, i=1,\cdots,m$, of the chemical species is given by the *balance laws*

$$\dot{x}=Sv \tag{2}$$

where S is an $m\times r$ matrix, called the *stoichiometric matrix*. The elements of the vector $v\in\mathbb{R}^r$ are commonly called the (reaction) *fluxes*. The stoichiometric matrix S, which consists of (positive and negative) integer elements, captures the basic conservation laws of the reactions. Consider again the first reversible reaction in (1)

$$\mathrm{Glu}+2\mathrm{NAD}+2\mathrm{ADP}\rightleftharpoons 2\mathrm{Pyr}+2\mathrm{NADH}+2\mathrm{ATP}, \tag{3}$$

where the species are {Glu, NAD, ADP, Pyr, NADH, ATP}. It has the stoichiometric matrix

$$S=\begin{bmatrix}-1 & -2 & -2 & 2 & 2 & 2\end{bmatrix}^T.$$

Although the stoichiometry does not fully determine the dynamics of the chemical reaction network (for this to be the case the vector of fluxes v needs to be expressed as a *reaction rate* $v=v(x)$) it already contains very useful information about the network dynamics, *independent* of the precise form of the reaction rate $v(x)$. For example, if there exists an m-dimensional row-vector k such that

$$kS=0$$

then the quantity kx is a *conserved quantity* for the dynamics $\dot{x}=Sr(x)$ for *all* possible reaction rates $v=r(x)$. Indeed, $\frac{d}{dt}kx=kSr(x)=0$. For a vector $k\in\mathbb{R}^m_+$ with nonnegative integer elements the quantity kx is commonly called a *conserved moiety*.

Geometrically, this means that for all possible fluxes the solutions of the differential equations $\dot{x}=Sv(x)$ starting from an initial state x_0 will always remain within the affine space $x_0+\mathrm{im}\,S$.

B. The complex graph

The structure of a chemical reaction network cannot be directly captured by an ordinary graph (since generally there are more than two chemical species involved in a reaction). Instead, we will follow an approach originating in the work of Horn & Jackson [11] and Feinberg [7], [8], introducing the space of *complexes*. The set of complexes of a chemical reaction network is simply defined as the union of all the different left- and righthand sides (substrates and products) of the reactions in the network.

For the reversible reaction networks in (1), the reactions entails four complexes, namely the substrates (reactants) Glu+2NAD+2ADP and Pyr+NADH, and the products 2Pyr+2NADH+2ATP and Lactate+NAD. Thus a product

complex of one reaction may be the substrate complex of another. Furthermore, a complex may be the product or substrate complex of more than one reactions.

The expression of the complexes in terms of the chemical species is formalized by an $m \times c$ matrix Z, whose α-th column captures the expression of the α-th complex in the m chemical species. For example, the column expressing the complex Glu+2NAD+2ADP in the reversible chemical reactions (3) is

$$\begin{bmatrix} 1 & 2 & 2 & 0 & 0 & 0 \end{bmatrix}^T.$$

Note that by definition all elements of the matrix Z are non-negative integers. It follows that the relation between the vector of concentrations of chemical species $x \in \bar{\mathbb{R}}^m_+$ and the vector $y \in \mathbb{R}^c$ expressing the amounts of all the complexes is $x = Zy$.

Since the complexes are left- and right-hand sides of the reactions they can be naturally associated with the vertices of a *directed graph* $\mathcal{G}$, with edges corresponding to the reactions, the complexes on the lefthand side of the reactions are called the substrate complexes and those on the righthand side of the reactions are called the product complexes. Formally, the reaction $\alpha \rightleftharpoons \beta$ between the α-th and the β-th complex defines a directed edge with tail vertex being the α-th complex and head vertex being the β-th complex. The resulting graph will be called the *complex graph*. Recall, see e.g. [2], that any directed graph is defined by its *incidence matrix* B. This is an $c \times r$ matrix, c being the number of vertices and r being the number of edges, with (ℓ, α)-th element equal to -1 if vertex ℓ is the tail vertex of edge α and 1 if vertex ℓ is the head vertex of edge α, while 0 otherwise.

Obviously, there is a close relation between the matrix Z and the stoichiometric matrix S. In fact, it is easily checked that

$$S = ZB, \tag{4}$$

with B the incidence matrix of the complex graph. For this reason we will call Z the *complex stoichiometric matrix*. Hence the relation $\dot{x} = Sv$, cf. (2), between the fluxes v through the chemical reaction network and the time-derivative of vector of chemical species x can be also written as

$$\dot{x} = ZBv \tag{5}$$

with Bv belonging to the space of complexes $\mathbb{R}^c$.

Geometrically this is summarized in the following diagram. Denote the space $\bar{\mathbb{R}}^m_+$ of *metabolites* (chemical species) by $\mathcal{M}$. Similarly, denote the linear space $\mathbb{R}^r$ of *reactions* by $\mathcal{R}$, and the linear space $\mathbb{R}^c$ of *complexes* by $\mathcal{C}$. Then we have

$$\begin{array}{c} \mathcal{R} \xrightarrow{B} \mathcal{C} \xrightarrow{Z} \mathcal{M} \\ \hline S \longrightarrow \end{array} \tag{6}$$

III. The dynamics of mass action kinetics chemical reaction networks

In this section we will derive a compact form for the dynamics of a chemical reaction network, whose reactions are described by *mass action kinetics*.

A. The general form of mass action kinetics

The dynamics of the concentration vector x (or equivalently, in case of a fixed volume, the vector n of mole numbers) is given once the internal fluxes v are specified as a function $v = v(x)$ of x, defining the *reaction rates*. The most basic model for specifying the reaction rates is *mass action kinetics*, defined as follows. For a reversible reaction networks with r reactions, the mass action rate of the n-th reaction with a substrate complex $\mathcal{S}$ and a product complex $\mathcal{P}$ is given as

$$v_n(x) = k_n^{\text{forward}} \prod_{i=1}^{m} x_i^{Z_{i\mathcal{S}}} - k_n^{\text{reverse}} \prod_{i=1}^{m} x_i^{Z_{i\mathcal{P}}}, \tag{7}$$

where $Z_{i\ell}$ is the (i,ℓ)-th element of the complex stoichiometric matrix Z, and $k_n^{\text{forward}}, k_n^{\text{reverse}}$ are the forward/reverse reaction constants of the n-th reaction, respectively. Then the mass action rate for the complete reactions is given by the vector $v(x) = \begin{bmatrix} v_1(x) & \cdots & v_r(x) \end{bmatrix}^T$.

This can be rewritten in the following way. Let $Z_{\mathcal{S}_n}$ and $Z_{\mathcal{P}_n}$ denote the columns of the complex stoichiometry matrix Z corresponding to the substrate and the product complexes in the n-th reaction. Using the operators Ln and Exp as defined in the Introduction, the mass action reaction equation (7) for the n-th reaction from a substrate complex $\mathcal{S}_n$ to a product complex $\mathcal{P}_n$ can be compactly written as

$$v_n(x) = k_n^{\text{forward}} \exp\left(Z_{\mathcal{S}_n}^T \operatorname{Ln}(x)\right) - k_n^{\text{reverse}} \exp\left(Z_{\mathcal{P}_n}^T \operatorname{Ln}(x)\right). \tag{8}$$

Based on the formulation in (8), we can describe the complete reaction networks as follows. For every $i, j = 1, \ldots, c$, denote by $a_{ij} = k_n^{\text{reverse}}$, $a_{ji} = k_n^{\text{forward}}$ if $(i,j) = (\mathcal{S}_n, \mathcal{P}_n)$, $n \in \{1, \ldots, r\}$ and $a_{ij} = 0$ elsewhere. Define the *weighted adjacency matrix* A of the complex graph as the matrix with (i,j)-th element $a_{ij}, i, j = 1, \cdots, c$. Furthermore, define the *weighted Laplacian* matrix L as the $c \times c$ matrix

$$L := \Delta - A \tag{9}$$

where Δ is the diagonal matrix whose (i,i)-th element is equal to the sum of the elements of the i-th column[1] of A. Then it can be verified that the dynamics $\dot{x} = ZBv(x)$ for the mass action rate equation vector $v(x)$ is equal to

$$\dot{x} = -ZL\operatorname{Exp}\left(Z^T \operatorname{Ln}(x)\right) \tag{10}$$

A similar expression, in less explicit form, was also obtained in [18].

B. Balanced mass action kinetics

A vector of concentrations $x^* \in \mathbb{R}^m_+$ is called an *equilibrium* for the dynamics $\dot{x} = Sv(x)$ if

$$Sv(x^*) = 0 \tag{11}$$

[1]Hence the sum of the elements of every column of L is zero. It follows that the definition of the weighted Laplacian matrix is slightly *different* from the one used in the analysis of the consensus algorithm. In this case Δ is defined as the diagonal matrix whose (i,i)-th element is equal to the sum of the elements of the i-th *row* of A, implying that the sum of the elements of every row of L is zero.

Furthermore, $x^* \in \mathbb{R}^m_+$ is called a *thermodynamic equilibrium* if

$$v(x^*) = 0 \tag{12}$$

Clearly, any thermodynamic equilibrium is an equilibrium for the dynamics, but not necessarily the other way around (since in general $S = ZB$ is not injective).

Necessary and sufficient conditions for the existence of a thermodynamic equilibrium can be derived in the following linear-algebraic way following [9]. These conditions are usually referred to as the *Wegscheider conditions*, generalizing the classical results of [21].

Consider the j-th reaction from substrate $\mathcal{S}_j$ to product $\mathcal{P}_j$, described by the mass action rate equation $\big($see (8)$\big)$

$$v_j(x) = k_j^{\text{forw}} \exp\left(Z_{\mathcal{S}_j}^T \text{Ln}(x)\right) - k_j^{\text{rev}} \exp\left(Z_{\mathcal{P}_j}^T \text{Ln}(x)\right)$$

Then $x^* \in \mathbb{R}^m_+$ is a thermodynamic equilibrium, i.e., $v(x^*) = 0$, if and only if

$$k_j^{\text{forw}} \exp\left(Z_{\mathcal{S}_j}^T \text{Ln}(x^*)\right) = k_j^{\text{rev}} \exp\left(Z_{\mathcal{P}_j}^T \text{Ln}(x^*)\right), \quad j = 1, \cdots, r \tag{13}$$

The equations (13), sometimes referred to as the *detailed balance equations*, can be rewritten as follows. Define the *equilibrium constant* K_j^{eq} of the j-th reaction as (assuming $k_j^{\text{rev}} \neq 0$)

$$K_j^{eq} := \frac{k_j^{\text{forw}}}{k_j^{\text{rev}}} \tag{14}$$

Then the detailed balance equations (13) are seen to be equivalent to

$$K_j^{eq} = \exp\left(Z_{\mathcal{P}_j}^T \text{Ln}(x^*) - Z_{\mathcal{S}_j}^T \text{Ln}(x^*)\right), \quad j = 1, \cdots, r \tag{15}$$

Collecting all reactions, and making use of the incidence matrix B of the complex graph, this amounts to the vector equation

$$K^{eq} = \text{Exp}\left(B^T Z^T \text{Ln}(x^*)\right) = \text{Exp}\left(S^T \text{Ln}(x^*)\right), \tag{16}$$

where K^{eq} is the r-dimensional vector with j-th element $K_j^{eq}, j = 1, \cdots, r$.

From here it is easy to characterize the existence of a thermodynamic equilibrium.

Proposition 3.1: There exists a thermodynamic equilibrium $x^* \in \mathbb{R}^m_+$ if and only if $k_j^{\text{forw}} > 0, k_j^{\text{rev}} > 0$, for all $j = 1, \cdots, r$, and furthermore

$$\text{Ln}\left(K^{eq}\right) \in \text{im}\, S^T \tag{17}$$

It also follows that once a thermodynamic equilibrium x^* is given, the set of *all* thermodynamic equilibria is described as follows.

Proposition 3.2: Let $x^* \in \mathbb{R}^m_+$ be a thermodynamic equilibrium, then the set of *all* thermodynamic equilibria is given by

$$\mathcal{E} := \{x^{**} \in \mathbb{R}^m_+ \mid S^T \text{Ln}\left(x^{**}\right) = S^T \text{Ln}\left(x^*\right)\} \tag{18}$$

For ease of exposition we will henceforth refer to mass action chemical networks possessing a thermodynamic equilibrium $x^* \in \mathbb{R}^m_+$ as *balanced mass action chemical networks*. As stated in Proposition 3.1, a necessary condition for the existence of a thermodynamic equilibrium is the fact that for all reactions the forward and reverse reaction constants are both strictly positive. Thus all reactions of a balanced reaction network need to be at least *reversible*.

The equation (13) allows us to define the *balanced reaction constant* of the n-th reaction as

$$\begin{aligned}\kappa_n(x^*) &:= k_n^{\text{forward}} \exp\left(Z_{\mathcal{S}_n}^T \text{Ln}(x^*)\right) \\ &= k_n^{\text{reverse}} \exp\left(Z_{\mathcal{P}_n}^T \text{Ln}(x^*)\right).\end{aligned}$$

It follows that the n-th reaction can be written as

$$v_n(x) = \kappa_n(x^*) \left[\exp\left(Z_{\mathcal{S}_n}^T \text{Ln}\left(\frac{x}{x^*}\right)\right) - \exp\left(Z_{\mathcal{P}_n}^T \text{Ln}\left(\frac{x}{x^*}\right)\right)\right].$$

Recall from the Introduction that the quotient vector $\frac{x}{z} \in \mathbb{R}^m$ is defined elementwise.

Let $\kappa_1(x^*), \cdots, \kappa_r(x^*)$ denote the equilibrium coefficients of all the r reactions corresponding to the rate equation equilibrium x^*. Define the $r \times r$ diagonal matrix of equilibrium coefficients

$$\mathcal{K}(x^*) := \text{diag}\big(\kappa_1(x^*), \cdots, \kappa_r(x^*)\big). \tag{19}$$

Then it follows that the mass action reaction rate vector of a balanced reaction network can be written as

$$v(x) = -\mathcal{K}(x^*) B^T \text{Exp}\left(Z^T \text{Ln}\left(\frac{x}{x^*}\right)\right). \tag{20}$$

and thus the dynamics of the vector of concentrations x is given as

$$\dot{x} = -ZB\mathcal{K}(x^*) B^T \text{Exp}\left(Z^T \text{Ln}\left(\frac{x}{x^*}\right)\right). \tag{21}$$

The matrix $B\mathcal{K}(x^*)B^T$ again defines a *weighted Laplacian* matrix for the complex graph, with weights given by the equilibrium coefficients $\kappa_1(x^*), \cdots, \kappa_r(x^*)$. Note that this is in general a *different* weighted Laplacian matrix than the one obtained before[2], cf. (9). In particular, a main difference is that the weighted Laplacian $B\mathcal{K}(x^*)B^T$ is necessarily *symmetric*. Among others, cf. [2], this implies that the Laplacian $B\mathcal{K}(x^*)B^T$ is in fact independent of the *orientation* of the graph. Thus we may replace any reaction $\mathcal{S} \rightleftharpoons \mathcal{P}$ by $\mathcal{P} \rightleftharpoons \mathcal{S}$ without altering the Laplacian $B\mathcal{K}(x^*)B^T$, in agreement with the usual understanding of a reversible reaction network. Note that the symmetrization of the Laplacian has been accomplished by the modification of $\text{Ln}(x)$ into $\text{Ln}\left(\frac{x}{x^*}\right)$.

Let us define, up to a constant, $\mu(x) := \text{Ln}(\frac{x}{x^*})$ as the chemical potential vector and

$$G(x) := x^T \left[\text{Ln}\left(\frac{x}{x^*}\right) - \mathbb{1}_m\right] + x^{*T} \mathbb{1}_m. \tag{22}$$

It can be immediately checked that

$$\frac{\partial G}{\partial x}(x) = \text{Ln}\left(\frac{x}{x^*}\right) = \mu(x). \tag{23}$$

[2]Also note that $\mathcal{K}(x^*)$, and therefore the Laplacian matrix, is dependent on the rate reaction equilibrium x^*.

Using G, it follows that the equations of a balanced chemical reaction network (21) can be equivalently written as

$$\dot{x} = -ZB\mathcal{K}(x^*)B^T\mathrm{Exp}\left(Z^T\frac{\partial G}{\partial x}(x)\right) \tag{24}$$

In the next section, we will employ $G(x)$ as a *Lyapunov function* for the chemical reaction network.

The *complex affinity* γ of the reaction network is defined as

$$\gamma := Z^T\mu. \tag{25}$$

A geometric interpretation of the equation (21) or (24) is as follows. Denote the dual space of the space of concentrations of chemical species $\mathcal{M} = \mathbb{R}^m_+$ by $\mathcal{M}^*$. Similarly, denote the dual space of $\mathcal{C} = \mathbb{R}^c$ by $\mathcal{C}^*$, and the dual of the space of reaction rates $\mathcal{R} = \mathbb{R}^r$ by $\mathcal{R}^*$. Define $v^* := B^T\mathrm{Exp}(\gamma)$ and $y := Bv(x, x^*)$. All the ingredients for the equation (21) are contained in the following diagram:

$$\begin{array}{ccccc} v \in \mathcal{R} & \xrightarrow{B} & y \in \mathcal{C} & \xrightarrow{Z} & x \in \mathcal{M} \\ \mathcal{K}(x^*) & | & & | & G(x,x^*) \\ v^* \in \mathcal{R}^* & \xleftarrow[B^T]{} & \gamma \in \mathcal{C}^* & \xleftarrow[Z^T]{} & \mu \in \mathcal{M}^* \end{array} \qquad \circlearrowleft \ \mathrm{Exp} \tag{26}$$

This clearly expresses the duality relations between all the variables involved. The concentration vector x and its time-derivative $\dot{x}$ are elements of the linear space $\mathcal{M}$ with conjugate vector, the chemical potential vector $\mu \in \mathcal{M}^*$. They are related by the Lyapunov function $G(x, x^*)$ as $\mu = \frac{\partial G}{\partial x}(x, x^*)$. Furthermore, the vector y is in the linear space $\mathcal{C}$, with conjugate vector the complex affinity γ. The relations between y and $\dot{x}$ and between μ and γ are dually given by $\dot{x} = Zy$, respectively $\gamma = Z^T\mu$. The vector of fluxes v is in the linear space $\mathcal{R}$, with conjugate vector $v^* := -\big(\mathcal{K}(x^*)\big)^{-1}v \in \mathcal{R}^*$. The added complication in the diagram is the map $\mathrm{Exp} : \mathcal{C}^* \to \mathcal{C}^*$, which introduces a discrepancy between v^* and $\alpha := -B^T\gamma = -S^T\mu$.

C. The linkage classes of the complex graph

The complex graph provides a number of tools for the analysis of reaction networks. Recall that for any directed graph [2]

$$\mathrm{rank}\, B = \mathrm{rank}\, L = m - \ell, \tag{27}$$

where m is the number of vertices of the graph, and ℓ is equal to the number of components[3] of the complex graph[4], the *linkage classes* in the terminology of [11], [7], [8].

[3]A directed graph is *connected* if there is a path (a number of un-oriented edges) between every two distinct vertices of the graph. The components of a directed graph are the maximal connected subgraphs.

[4]In general, L and its eigenvalues serve as a measure for the connectedness of the complex graph [2].

Furthermore, if there is one linkage class in the network (i.e., the graph is connected and $\mathrm{rank}\, B = \mathrm{rank}\, L = m-1$), then

$$\ker L = \ker B^T = \mathrm{span}\, \mathbb{1}_c \tag{28}$$

where as before $\mathbb{1}_c$ is the c-dimensional vector with elements all equal to 1.

D. Deficiency

A crucial notion to relate the complex graph with the stoichiometry, as introduced in the work of Feinberg [7], is the notion of *deficiency*.

Definition 3.3: The deficiency of a chemical reaction network with complex stoichiometric matrix Z and incidence matrix B is defined as

$$\delta := \mathrm{rank}\, B - \mathrm{rank}\, ZB = \mathrm{rank}\, B - \mathrm{rank}\, S \geq 0 \tag{29}$$

A reaction network is said to have *zero-deficiency* if $\delta = 0$. Note that zero-deficiency is is equivalent to

$$\ker Z \cap \mathrm{im}\, B = 0, \tag{30}$$

or to the mapping

$$Z : \mathrm{im}\, B \subset \mathbb{R}^c \to \mathbb{R}^m \tag{31}$$

being *injective*. Hence in the zero-deficiency case there is a one-to-one correspondence between the vector of chemical species $x \in \mathrm{im}\, S \subset \mathcal{M}$ and the vector of complexes $y \in \mathrm{im}\, B \subset \mathcal{C}$. Many chemical reaction networks are zero-deficient, although with growing complexity (especially in biochemical networks) deficiency greater than zero is likely to occur.

E. Equilibria of reversible networks and asymptotic stability

In this section, we focus our attention to the properties of equilibria of balanced chemical reaction networks. The first result that we provide in this section has been already stated and proved in [8]. We make use of the formulation of the dynamics of balanced reaction networks $\big($equation (21)$\big)$, in order to give a simpler proof of and a deeper insight into the result as compared to the proof of the same result provided in [8]. This result gives a characterization of all equilibrium points of a given reversible reaction network in terms of a known kinetic equilibrium. Given below is the first result of this section.

Theorem 3.4: Consider a balanced chemical reaction network $\dot{x} = Sv = ZBv$ with m species and r reactions governed by mass action kinetics, with thermodynamic equilibrium x^*, i.e., $v(x^*) = 0$, described as in (21). Then the set of all equilibria is equal to the set $\mathcal{E} := \{x^{**} \in \mathbb{R}^m_+ \mid S^T\mathrm{Ln}(x^{**}) = S^T\mathrm{Ln}(x^*)\}$ of thermodynamic equilibria given in (18).

For proof, we refer to [19, Theorem 4.1].

Following Theorem 3.4, we can define the space of equilibrium points for a reversible mass action chemical network in (21) by $\mathcal{E} := \{\xi \in \mathbb{R}^m_+ | S^T\mathrm{Ln}\left(\frac{\xi}{x^*}\right) = 0\}$.

Now consider the dynamical equations of a balanced reaction network as given by equation (24):

$$\dot{x} = -ZB\mathcal{K}(x^*)B^T\mathrm{Exp}\left(Z^T\frac{\partial G}{\partial x}(x)\right)$$

where G is defined as before:

$$G(x) := x^T\left[\mathrm{Ln}\left(\frac{x}{x^*}\right) - \mathbb{1}_m\right] + x^{*T}\mathbb{1}_m. \qquad (32)$$

Using Theorem 3.4 and G as the Lyapunov function, we show below that the system (21) is globally asumptotically stable with respect to $\mathcal{E}$, i.e., $\mathcal{E}$ is globally attractive.

Theorem 3.5: Consider a balanced mass action reaction network given by (21) or, equivalently, by (24). Then for every initial condition $x(0) \in \mathbb{R}^m_+$, the species concentration x converges for $t \to \infty$ to $\mathcal{E}$.

For proof, we refer to [19, Theorem 4.2].

F. Equilibrium concentration corresponding to an initial concentration

In this section, we show that for every initial concentration vector $x_0 \in \mathbb{R}^m_+$, the solution trajectory of (21) converges to a *unique* thermodynamic equilibrium in $\mathcal{E}$. Our reasoning is very similar to the proof of zero-deficiency theorem provided in [8] and is based on the following proposition in there. Recall from the Introduction that the product $x \cdot z \in \mathbb{R}^m$ is defined as the element-wise product $(x \cdot z)_i = x_i z_i$, $i = 1, \cdots, m$.

Proposition 3.6: Let U be a linear subspace of $\mathbb{R}^m$, and let $x^*, x_0 \in \mathbb{R}^m_+$. Then there is a unique element $\mu \in U^\perp$, such that $\left(x^* \cdot \mathrm{Exp}(\mu) - x_0\right) \in U$.

For proof, see [8, Proposition B.1, pp. 361-363].

Theorem 3.7: Consider the balanced chemical reaction network (21). Then for every $x_0 \in \mathbb{R}^m_+$, there exists a unique $x_1 \in \mathcal{E}$ such that the solution trajectory of (21) starting from x_0 converges for $t \to \infty$ to x_1. Hence there exists a surjective map $\chi : \mathbb{R}^m_+ \to \mathcal{E}$ that assigns to every initial state its asymptotic thermodynamic equilibrium[5].

We refer to [19, Theorem 4.5] for the proof.

Theorem 3.7 is closely related to the property that the asymptotic consensus value in consensus dynamics is a function of the initial state. In fact, the surjective map $\chi : \mathbb{R}^m_+ \to \mathcal{E}$ which assigns to every initial state its asymptotic equilibrium is similar to the χ-function in the χ-consensus algorithm of [3].

IV. Conclusions

In this paper we have provided a compact, geometric, formulation of the dynamics of mass action chemical reaction networks possessing a thermodynamic equilibrium. This formulation clearly exhibits both the structure of the complex graph and the stoichiometry. Exploiting this formulation we were able to recover, for the balanced mass action kinetics chemical reaction networks, some of the results in the fundamental work [11], [10], [7], [8] in a simple and insightful way, without having to rely on the properties of deficiency zero or one.

[5]Following a similar argument as in [18, Theorem 6] (which basically deals with weakly-reversible zero-deficiency chemical networks) the map χ can be shown to be real-analytic.

References

[1] D. Angeli, P. de Leenheer, E. Sontag, "Graph-theoretic characterizations of monotonicity of chemical networks in reaction coordinates," J. Math. Biol., vol. 61, pp. 581–616, 2010.

[2] B. Bollobas, *Modern Graph Theory*, Graduate Texts in Mathematics 184, Springer, New York, 1998.

[3] J. Cortés, "Distributed algorithms for reaching consensus on general functions," Automatica, vol. 44, no. 3, pp. 726-737, 2008.

[4] F. Couenne, C. Jallut, B. Maschke, P.C. Breedveld, M. Takayout, "Bond graph modelling for chemical reactors", *Mathematical and Computer Modelling of Dynamical Systems*, 12(2), pp. 159–174, 2006.

[5] G. Craciun, M. Feinberg, "Multiple equilibria in complex chemical reaction networks: II. The species-reaction graph", *SIAM J. Appl. Math.*, 66(4), pp. 1321–1338, 2006.

[6] P. De Leenheer, E. Sontag, D. Angeli, "A Petri net approach to the study of persistence in chemical reaction networks, *Mathematical Biosciences*, 210, pp.: 598 - 618, 2007.

[7] M. Feinberg, "Chemical reaction network structure and the stability of complex isothermal reactors -I. The deficiency zero and deficiency one theorems", *Chemical Engineering Science*, 43(10), pp. 2229–2268, 1987.

[8] M. Feinberg, "The existence and uniqueness of steady states for a class of chemical reaction networks", *Arch. Rational Mech. Anal.*, 132, pp. 311–370, 1995.

[9] M. Feinberg, "Necessary and sufficient conditions for detailed balancing in mass action systems of arbitrary complexity", *Chemical Engineering Science*, 44(9), pp. 1819–1827, 1989.

[10] F.J.M. Horn, "Necessary and suffcient conditions for complex balancing in chemical kinetics", *Arch. Rational Mech. Anal.*, 49, pp. 172–186, 1972.

[11] F. Horn, R. Jackson, "General mass action kinetics", *Arch. Rational Mech. Anal.*, 47, pp. 81–116, 1972.

[12] R. Olfati-Saber, J.A. Fax, R.M. Murray, "Consensus and cooperation in networked multi-agent systems", *Proceedings of the IEEE, 95*, No.1, 2007.

[13] G. Orosz, J. Moehlis, R.M. Murray, "Controlling biological networks by time-delayed signals," Phil. Trans. Roy. Soc. A, vol. 368, pp. 439-454, 2010.

[14] J.F. Oster, A.S. Perelson, A. Katchalsky, "Network dynamics: dynamic modeling of biophysical systems", *Quarterly Reviews of Biophysics*, 6(1), pp. 1-134, 1973.

[15] J.F. Oster, A.S. Perelson, "Chemical reaction dynamics, Part I: Geometrical structure", *Archive for Rational Mechanics and Analysis*, 55, pp. 230-273, 1974.

[16] H. G. Othmer, *Analysis of Complex Reaction Networks*, Lecture Notes, School of Mathematics, University of Minnesota, December 9, 2003.

[17] D.A. Paley, N.E. Leonard, R. Sepulchre, D. Grünbaum, J.K. Parrish, "Oscillator models and collective motion," IEEE Control Systems Magazine, pp. 89–105, August 2007.

[18] E.D. Sontag, "Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction," IEEE Trans. Automat. Contr., vol. 46, no. 7, pp. 1028–1047, 2001.

[19] A.J. van der Schaft, S. Rao, B. Jayawardhana, "On the mathematical structure of balanced chemical reaction networks governed by mass action kinetics," submitted. Pre-print http://arxiv.org/abs/1110.6078

[20] A.J. van der Schaft, B.M. Maschke, "Discrete conservation laws and port-Hamiltonian systems on graphs and complexes", submitted for publication, 2011, arXiv.

[21] R. Wegscheider, "Über simultane Gleichgewichte und die Beziehungen zwischen Thermodynamik und Reaktionskinetik homogener Systeme", *Zetschrift für Physikalische Chemie*, 39, pp. 257–303, 1902.

[22] Y. Yuan, G-B. Stan, S. Warnick, J. Goncalves, "Robust dynamical network structure reconstruction," Automatica, vol. 47, no. 6, pp. 1230-1235, 2011.